PCT requirement with the standard in this patent application. MPEP 803.02 and In re Haas, 580 F.2d 461, 198 USPQ 334 [CCPA 1978] states that "unity of invention" is the standard applied to restriction of Markush claims. Claims 5, 9, 14, 18 and 20 are all examples of Markush claims.

As stated in the prior response, the Examiner has failed to meet a *prima facie* showing for the requirement of restriction in that no reasons or examples were cited as to the need for restriction. Applicants hereby reserve the right to petition the restriction requirement.

B. Double Patenting

Claims 1 - 7, 9 - 10, 12 - 15 and 17 - 20 stand rejected over the judicially created doctrine of obviousness type double patenting over certain claims in U.S. Patent Nos. 6,372,195; 6,258,339; 5,695,741; 5,639,443; 5,798,091; 5,804,162; and 6,193,952. Because the scope of the present claims as allowed is not yet known, applicants respectfully request the right to revisit the issue after the claims have been formally allowed.

C. Rejection of the claims over Schneider in view of Tickner

Claims 1 - 6, 9 - 10, 13 - 15, 17 - 18 and 20 stand rejected under 35 USC 103(a) as being unpatentable over Schneider in view of Tickner. Applicants respectfully disagree.

The Examiner asserts that Schneider teaches the use of C_4F_{10}. Actually, Schneider does not disclose the use of C_4F_{10} but teaches the use of octafluorocyclobutane which is a ring structure rather than a straight chained structure and has the molecular formula C_4F_8.

Schneider mentions gas mixtures in general terms but never teaches in any of the Examples a gas mixture containing a fluorocarbon gas. In contrast to the assertion in the Office Action, column 5, lines 50 - 56 does not mention the fluorocarbon gas and a "secondary gas such as air which contains oxygen, nitrogen, CO2 and the like." The list of gases in column 5, lines 50 - 56 is actually referring to the prior art:

> ....in a second embodiment as said before, one will effect the full preparation of this suspension of the echogenic additives starting with the usual precursors thereof (starting materials), as recited in the prior art and operating according usual means of said prior art, but in the presence of the desired gases or mixture of gases according to the invention instead of that of the prior art which usually recites gases such as air, nitrogen, CO_2 and the like.

Example 7 describes the creation of "echo-generating agents" according to a "two step preparation mode" in contrast to the "one-step preparation mode" of Example 1 for the purpose of determining the microbubble's resistance to pressure. According to the teachings of Example 7, "the air in some of the samples were replaced by other gases in the gas-exchange sweep method at ambient pressure." The "gas exchange sweep method" or "gas exchange technique" is described on column 4, lines 53 - 64. This method is described as a:

> ... two step route consisting of (1) making the microvesicles from the appropriate starting materials by any suitable conventional technique in the presence of any suitable gas, and (2) replacing this gas originally used (first gas) for preparing the microvesicles with a new gas (second gas) according to the invention (gas exchange technique).

Example 7 is for the express purpose of determining the improved resistance to pressure in microbubbles by substituting air for another gas such as SF_6 (see A18 and A19). The results in Example 7 utilizing gases such as SF_6 instead of air demonstrate a significant improvement over resistance to pressure therefore leading one to the conclusion that substitution with the second gas SF_6 provides a superior microbubble for *in vivo* diagnostic imaging. However, there is no mention that A18 or A19 or any other microbubble involves a mixture of gases involving a fluorocarbon. Due to the purpose of the experiment, which is determining what gases provide a more superior contrast agent than an air microbubble, the end result desired to be achieved would be complete replacement of air with the selected gas, in this case, SF_6. Without any express mention of a gas mixture in Example 7, it must be presumed that complete replacement was achieved. In fact, the teachings of Example 7 would teach away from the idea of gas mixtures and certainly no "fluorocarbon gas and modifier gas" is taught as required by claim 1 of the

present application.

In Example 8, bubble suspensions are created partially in a different manner than in Example 7 (three way valve using two syringes) and substituting various lecithins. However, the gases are substituted according to the teachings of Example 4 and there is no reason, according to the specification, to believe that gas mixtures of microbubbles are created.

The Examiner also states that because the fluorocarbon is the same in the prior art as that claimed in the present invention and there are similar modifier gases, that the functional characteristics of the claimed invention would be inherent. However, as stated previously, the fluorocarbon is not the same as in the prior art and there is no express teachings of gas mixtures in Schneider involving a fluorocarbon.

Tickner (U.S. Patent No. 4,265,251) does not supply the missing elements lacking in Schneider. Tickner is directed to an invention for measuring pressure (i.e., blood pressure) in a vessel such as the cardiovascular system. Solid precursors (80% sucrose / 20% lactose) with a hollow interior filled with a gas (e.g., carbon dioxide) are injected into a liquid (the blood stream) wherein the solid wall is broken or dissolved (see columns 3 and 4). In column 6, lines 62 - 66, it is stated that "[o]ther gases which are useful include nitrogen, oxygen, argon, xenon, air, methane, freon, ether and even carbon monoxide ...." The Examiner states that "Tickner shows that for the purpose of ultrasonic contrast agents, gases such as oxygen, nitrogen, and Freons are substantially interchangeable and are functional equivalents." Applicants respectfully disagree.

Tickner makes absolutely no showing that "oxygen, nitrogen and Freons" are substantially interchangeable or are functional equivalents. First, the statement is not true. Schneider demonstrates in great detail how air and certain fluorine containing compounds (e.g., SF_6) produce very different types of microbubbles having very different physical properties such as differing resilience to pressure, solubility and size. Further, the applicant's own application explains the differences between modifier gases and gas osmotic agents and how each acts in microbubbles. Further, Tickner provides no examples concerning microbubbles other than those containing carbon dioxide. Tickner simply mentions in column 6 that "other gases" can be used

and provides a list of gases. However, that does not mean such gases are interchangeable with carbon dioxide and Tickner provides no teaching of this. Also, the only mention of ultrasound imaging in Tickner is in column 7, as an after thought. Tickner is mainly concerned with measuring pressure of liquids in a container.

Schneider in view of Tickner does not obviate the subject matter of claim 1. Nowhere in Schneider or in Tickner is the subject matter of claim 1 taught or suggested and withdrawal of the rejection is respectfully requested.

D. Rejection of the claims over Schneider in view of Unger

Claims 1 -6, 9 - 10, 13 - 15, 17- 18 and 20 stand rejected under 35 USC 103(a) as being unpatentable over Schneider in view of Unger (U.S. Patent No. 5,205,290).

The Schneider reference has been previously discussed.

Unger teaches an aqueous suspension of low density microspheres made from inorganic compounds and methods of making the compounds. The plastic microspheres of Unger are suspended in an aqueous solution, a thickening agent and suspending agent is added to the aqueous solution to provide a uniform suspension, the aqueous solution is ingested by a patient and provides a low density aqueous solution that is useful for computed tomography. The Examiner states that "Unger specifically teaches the use of perfluorocarbons as those having between 1 and about 9 carbon atoms especially C_4F_{10}. Accordingly, Unger teaches the *in vivo* administration of oxygen and perfluorobutane as gas expanding compounds within microspheres of his contrast agents." Applicants respectfully disagree.

Unger teaches the use of certain "volatile liquids" in a heat expansion process in order to expand the dense, commercially available, Expancel microspheres. The microspheres have a volatile liquid in its interior and "the microsphere is then heated, plasticising the microsphere and volatilizing the gas, causing the microsphere to expand to up to about several times its original size." Col. 3, lines 57 - 60. One volatile liquid is stated to be perfluorobutane (C_4F_{10}).

There are several problems with the use of Unger as a reference in the rejection of the

claims. Unger's microspheres could not possibly be used in ultrasound imaging in that they would be lethal if injected into the bloodstream (due to their large size of 50 microns and their composition). The type of imaging described in Unger is CT imaging, a very different kind of imaging in comparison to ultrasound imaging.

Further, there is absolutely no reason to believe that any perfluorobutane would remain in the microsphere after the expansion process. The volatile liquids are used to expand the microsphere. Once the microsphere are heated with a temperature high enough to plasiticize the microsphere, the perfluorobutane would be boiled off and would escape into the atmosphere. There is no reason to believe it would remain in the microsphere after the heating step. Further, there would be no reason to believe that there is any oxygen in the microsphere after expansion, aside from that which is present in air. The claimed invention also requires that the "microbubble grow and shrink to maintain osmotic equilibrium with the physiological gas saturation of the surrounding external medium." The plastic microspheres of Unger, once cooled after the heat expansion process and handled as dry rigid microspheres, would be hard plastic and could not "grow and shrink" as required by the claims.

The deficiencies of Schneider were stated in reference to the previous rejection. Schneider does not teache a mixture of gases containing a fluorocarbon gas and a modifier gas wherein the microbbubles grow and shrink to obtain osmotic stabilization. Unger also does not teach a microbubble with a fluorocarbon gas and a modifier gas but instead teaches hard plastic microspheres for use in aqueous solutions for ingesting in CT scans. Thus, applicants respectfully request withdrawal of the rejection.

Applicants hereby respectfully request a two month extension of time which is requested by separate petition. If there are any questions, applicants' attorney can be reached at the

telephone number stated below.

Respectfully submitted,

Dated: 3/19/04

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